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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/163,648	09/30/1998	SUSAN L. ACTON	MIA-025.02	5728

7590 03/24/2004

INTELLECTUAL PROPERTY GROUP
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EXAMINER	
GUPTA, ANISH	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/163,648	ACTON ET AL.	
	Examiner	Art Unit	
	Anish Gupta	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-16 and 44-60* is/are pending in the application.

4a) Of the above claim(s) *44 and 60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-16 and 45-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-13-00*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Election/Restrictions

1. Applicant's election without traverse of Group II, claims 2-16, in the response dated 12-29-03 is acknowledged. Applicants cancelled claims 1, 17-43.

Newly submitted claim 44-60 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Claims 44 and 60 are drawn to an antibody, which would qualify under a new group, Group VIII. An antibody is structurally distinct from the polypeptide of Group II.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 44 and 60 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

2. The information disclosure statement filed 7-26-00 and 1-25-99 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Applicants are requested to submit the documents disclosed in the information disclosure statement in the "OTHERS" (the publications instead of the so the references can be considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 10 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims state that the polypeptide claimed binds to a "target peptide." It is unclear what peptide would constitute a "target peptide." That is, without the polypeptide binding to a "target" one would not know if a given peptide would be a "target peptide." Thus, one could not determine the meets and bounds of the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 2-16 and 45-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not

sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn amino acid sequences having an amino acid identity of at least about 90% with the entire amino acid sequence set forth in SEQ ID NO:2. The statement of % identity with regards to the native sequence renders the claim a generic claim since it encompasses an enormous number of species with potentially wide diverse properties. A 90% variant of SEQ. ID. 2 has approximately 81 different amino acids relative to the native sequence. Thus a variant of at least 90% would include, at the very least, every species having between 1 and 81 amino acid changes from 20 naturally amino acids. The generic statement of 90% not provide ample written description for the compounds since the claims do not describe a singe structural feature that is common to the all of the species. One cannot readily obtain the structural properties necessary to achieve the functional characteristics claimed.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable the claims are broad generic with respect all possible peptides encompassed by the claims. The possible structural variations are limitless to any class of polymer with any biomolecule. The claims recite that the

polypeptide functions in having the bioactivity of an ACE-2 polypeptide, binds to angiotensin I, "lacks the ability to hydrolyze angiotensin I into angiotensin," "binds to kinetensin," and "lacks the ability to hydrolyze kinetensin into kinetensin." However, it must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds. That is to say, it is unclear what portion of the structure is necessary to maintain the desired function. It is known that proteins fold and a single amino acid can have deleterious effects upon the folding and activity of the peptide. Even though a protein may have 90% identity, the difference in amino acid sequences would be expected to different secondary structures and have divergent biological activity, especially if the change was made in the active region of the peptide.

The specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of homologous peptides. The specification is not limited to polypeptides that share a common core. There is no disclosure a polypeptide with 90% homology that has the capability of having the bioactivity of an ACE-2 polypeptide, binds to angiotensin I, "lacks the ability to hydrolyze angiotensin I into angiotensin," "binds to kinetesin," and "lacks the ability to hydrolyze kinetensin into kinetensin." The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals

appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

5. Claims 2-16 and 45-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is relates to the Angiotensin Converting Enzyme-2.

(2) The state of the prior art

The art discloses the sequence of Angioetensin Converting Enzyme-2 in the human for both the nucleic acid and the protein.

(3) The relative skill of those in the art

The relative skill of the those in the art is high.

(4) The predictability or unpredictability of the art

As with all peptides in peptide chemistry, the activity of a peptide is dependant upon its structure and its ability to fold properly. It is known in the art that computer models assist in the research, however they are not are not an absolute prediction tool for the activity of the compound. For example, in peptide chemistry Ngo et al. teach that for proteins and peptides, a " 'Direct' approach to structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task." (see page 493 in Ngo et al.) Accordingly, it is not known if an efficient algorithm for predicting the structure exist for a protein or peptide from its amino acid alone (see page 492 in Ngo et al.). Similarly the Science article also states that although computers can be used to design drugs, "for the most part technicians must still screen many, many compounds to find their magic bullets." (see page 441). The article concludes that computer models are not an effective method of determining drug activity. "Even modest gains in the ability to predict drug activity from structural data will be enough to delight some computational biologist. 'Developing drugs is a vague science in which you synthesize a large number of compound." (See page 441).

(5) The breadth of the claims

The claims are extremely broad. The claims are drawn amino acid sequences having an amino acid identity of at least about 90% with the entire amino acid sequence set forth in SEQ ID NO:2. The statement of % identity with regards to the native sequence renders the claim a generic claim since it encompasses an enormous number of species with potentially wide diverse properties. A 90% variant of SEQ. ID. 2 has approximately 81 different amino acids relative to the native sequence. Thus a variant of at least 90% would include, at the very least, every species having between 1 and 81 amino acid changes from 20 naturally amino acids.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples

The specification states that the peptides claimed have the same activity as SEQ ID. NO. 2. Thus, a percent homolog of SEQ. ID. NO.2 has the capability of having the bioactivity of an ACE-2 polypeptide, binds to angiotensin I, "lacks the ability to hydrolyze angiotensin I into angiotensin," "binds to kinetesin," and "lacks the ability to hydrolyze kinetensin into kinetensin." The amount of guidance given is in the percent homolog of SEQ ID. NO. 2 is minimal. The specification does not provide any specific examples that would demonstrate that ANY at least 90% homolog of the SEQ. ID. NO.2 retains the desired activity. Indeed, the specification does not provide any examples that would demonstrate any conservatively substituted peptide, including substitution with a non-naturally occurring amino acid, would have the same receptor recognition and binding activity as the native peptide.

As stated above, the activity of the compounds is solely based on the data obtained from computer models. As stated above, the art is skeptical of associating activity for a peptide based on structure alone. Both Rudinger et al. and Ngo et al. indicate that computation hardware and general

knowledge of peptide chemistry fail to provide guidance as to the activity of any given peptide. The art also indicates that computer models are also insufficient to provide guidance and give a prediction of activity. Although computers can be used to design drugs, "for the most part technicians must still screen many, many compounds to find their magic bullets." (see page 441). The article concludes that computer models are not an effective method of determining drug activity. "Even modest gains in the ability to predict drug activity from structural data will be enough to delight some computational biologist. 'Developing drugs is a vague science in which you synthesize a large number of compound." (See page 441). Moreover it is stated computers are unable at this point to design a drug from scratch (see page 441). These articles make these conclusions for any compound regardless of conservative or non-conservative substitutions. Indeed, peptide chemistry is replete with examples that demonstrate a single point mutation in a native sequence adversely affects activity. Here, Applicants the claims not only ask for single point mutations but numerous mutation throughout the amino acid sequence. None of these mutations have been demonstrate in the present application. Although working examples are not required, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals

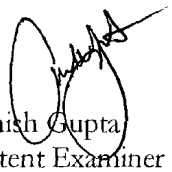
or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases."

(8) The quantity of experimentation necessary

Since, the is uncertain to predict the different aspects of biological activity, one of ordinary skill in the art would be burdened with undue painstaking experimentation study to determine if the compounds of the claimed invention would contain be active as claimed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can normally be reached on (571) 272-0961. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Anish Gupta
Patent Examiner
March 17, 2004